US Package Insert **FDA/MPI Finalized** **May 13, 2003**

Millennium Pharmaceuticals, Inc.

VELCADE™ (bortezomib) for Injection

Prescribing Information

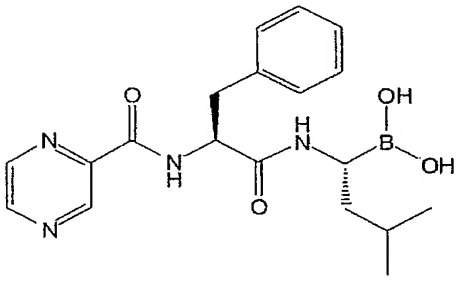
DESCRIPTION

VELCADE™ (bortezomib) for Injection is an antineoplastic agent available for intravenous injection (IV) use only. Each single dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl]boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is; $C_{19}H_{25}BN_4O_4$ The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8mg/mL in a pH range of 2-6.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted

proteolysis which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in non-clinical tumor models, including multiple myeloma.

Pharmacokinetics

Following intravenous administration of 1.3 mg/m^2 dose, the median estimated maximum plasma concentration of bortezomib was 509 ng/mL (range=109-1300 ng/mL) in eight patients with multiple myeloma and creatinine clearance values ranging from 31-169 mL/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to 15 hours at doses ranging from 1.45 to 2.00 mg/m^2 in patients with advanced malignancies. The pharmacokinetics of bortezomib as a single agent have not been fully characterized at the recommended dose in multiple myeloma patients.

Distribution

The distribution volume of bortezomib as a single agent was not assessed at the recommended dose in patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination

The pathways of elimination of bortezomib have not been characterized in humans.

Special Populations

Age, Gender, and Race: The effects of age, gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment: No pharmacokinetic studies were conducted with bortezomib in patients with hepatic impairment **(see PRECAUTIONS)**.

Renal Impairment: No pharmacokinetic studies were conducted with bortezomib in patients with renal impairment. Clinical studies included patients with creatinine clearances values ranging from 13.8 to 220 mL/min **(see PRECAUTIONS)**.

Pediatric: There are no pharmacokinetic data in pediatric patients.

Drug Interactions:

No formal drug interaction studies have been conducted with bortezomib.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 **(see PRECAUTIONS)**.

Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of > 30 μM (> 11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50}=18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme.

Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

CLINICAL STUDIES

Clinical Study in Relapsed and Refractory Multiple Myeloma

The safety and efficacy of VELCADE were evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Baseline patient and disease characteristics are summarized in **Table 1**.

An IV bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles. The study employed dose modifications for toxicity **(see DOSAGE AND ADMINISTRATION)**. Patients who experienced a response to VELCADE treatment were allowed to continue VELCADE treatment in an extension study.

Table 1: Summary of Patient Population and Disease Characteristics *

	N=202
Patient Characteristics:	
Median Age in Years (Range)	59 (34,84)
Gender: Male/Female	60%/40%
Race: Caucasian/Black/Other	81%/10%/8%
Karnofsky Performance Status Score ≤ 70	20%
Hemoglobin <100 g/L	44%
Platelet count <75 x 10^9/L	21%
Disease Characteristics:	
Type of myeloma (%): IgG/IgA/Light chain	60%/24%/14%
Median β_2-microglobulin (mg/L)	3.5
Median Creatinine Clearance (mL/min)	73.9
Abnormal Cytogenetics	35%
Chromosome 13 Deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any Prior Steroids, e.g., dexamethasone, VAD	99%
Any Prior Alkylating Agents, e.g., MP, VBMCP	92%
Any Prior Anthracyclines, e.g., VAD, mitoxantrone	81%
Any Prior Thalidomide Therapy	83%
Received at Least 2 of the Above	98%
Received at Least 3 of the Above	92%
Received All 4 of the Above	66%
Any Prior Stem Cell Transplant /Other High-dose Therapy	64%
Prior Experimental or Other Types of Therapy	44%

*Based on number of patients with baseline data available

Responses to VELCADE alone are shown in **Table 2**. Response rates to VELCADE alone were determined by an independent review committee (IRC) based on criteria published by Blade and others[1]. Complete response required < 5% plasma cells in the marrow, 100% reduction in M protein, and a negative immunofixation test (IF-). Response rates using the SWOG criteria are also shown. SWOG response required a ≥ 75% reduction in serum myeloma protein and/or ≥ 90% urine protein[2]. A total of 188 patients were evaluated for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC. Five patients were excluded from the efficacy analyses because they had minimal prior therapy.

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m^2. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study, while

33 % of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of VELCADE treatment beyond confirmation. The mean number of cycles administered was six.

The median time to response was 38 days (range 30 to 127 days).
The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

Table 2: Summary of Disease Outcomes

Response Analyses (VELCADE monotherapy) N=188	N (%)	(95% CI)
Overall Response Rate (Blade) (CR + PR)	52 (27.7%)	(21, 35)
Complete Response(CR)[1]	5 (2.7%)	(1, 6)
Partial Response(PR)[2]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	**365 Days**	**(224, NE)**

[1] **Complete response** required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

[2] **Partial Response** requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

[3] **Clinical Remission (SWOG)** required ≥75% reduction in serum myeloma protein and/or ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

In this study, the response rate to VELCADE was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities.

A small dose-response study was performed in 54 patients with multiple myeloma received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

INDICATIONS AND USAGE

VELCADE™ (bortezomib) for Injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

The effectiveness of VELCADE is based on response rates **(see CLINICAL STUDIES section)**. There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.

WARNINGS

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Pregnancy Category D

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory, although cases of mixed sensori-motor neuropathy have also been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening during treatment with VELCADE. Patients should be monitored for symptoms of

neuropathy, such as a burning sensation, hyperesthesia, hypesthesia, paresthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE **(see DOSAGE AND ADMINISTRATION)**. Limited follow-up data regarding the outcome of peripheral neuropathy are available. Of the patients who experienced treatment emergent neuropathy more than 70% had previously been treated with neurotoxic agents and more than 80% of these patients had signs or symptoms of peripheral neuropathy at baseline **(Also see ADVERSE REACTIONS)**.

Hypotension: VELCADE treatment can cause orthostatic/postural hypotension in about 12% of patients. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids.

Gastrointestinal Adverse Events: VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting **(see ADVERSE REACTIONS)** sometimes requiring use of antiemetics and antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

Thrombocytopenia: Thrombocytopenia, which occurred in about 40% of patients throughout therapy, was maximal at day 11 and usually recovered by the next cycle. Complete blood counts including platelet counts should be frequently monitored throughout treatment. Onset is most common in Cycles 1 and 2 but can continue throughout therapy. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE induced thrombocytopenia. VELCADE treatment may be temporarily discontinued if patients experience Grade 4 thrombocytopenia. VELCADE may be reinitiated at a reduced dose after resolution of thrombocytopenia **(see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS)**.

Patients with Hepatic Impairment:

Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with VELCADE.
(see CLINICALPHARMACOLOGY/Pharmacokinetics-Special Populations)

Patients with Renal Impairment:

No clinical information is available on the use of VELCADE in patients with creatinine clearance values less than 13 mL/min and patients on hemodialysis. These patients should be closely monitored for toxicities when treated with VELCADE **(see CLINICAL PHARMACOLOGY/Pharmacokinetics-Special Populations)**.

Animal Toxicity Findings:

Cardiovascular toxicity

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12-14 hours post dose. Doses ≥ 1.2 mg/m^2 induced dose proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration

In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1 week rest) toxicities observed included severe anemia and thrombocytopenia, gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

Information for Patients

Physicians are advised to discuss the following with patients to whom VELCADE will be administered.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability: Since VELCADE may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension, diplopia or blurred vision, patients should be cautious when operating machinery, including automobiles.

Pregnancy/Nursing: Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with VELCADE.

Dehydration/Hypotension: Since patients receiving VELCADE therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Concomitant Medications: Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

Peripheral Neuropathy: Patients should be instructed to contact their physician if they experience new or worsening symptoms of peripheral neuropathy **(see PRECAUTIONS and DOSAGE AND ADMINISTRATION)**.

Drug Interactions

No formal drug interaction studies have been conducted with VELCADE.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate for cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Patients who are concomitantly receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy **(see CLINICAL PHARMACOLOGY/Pharmacokinetics-Drug Interactions)**.

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

There have been several SAE reports since filing. These reports were submitted to the IND. If the Agency feels this information is unnecessary, the language can be removed.

Drug Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at doses ≥ 0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2. VELCADE could have a potential effect on either male or female fertility.

Pregnancy Category D (see **WARNINGS**)

Nursing Mothers

It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VELCADE, women should be advised against breast feeding while being treated with VELCADE.

Pediatric Use:

The safety and effectiveness of VELCADE in children has not been established.

Geriatric Use:

Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%) of patients aged 65 years or older experienced responses versus 32% in patients under the age of 65. Across the 256 patients analyzed for safety, the incidence of Grade 3 or 4 events reported was 74%, 80%, and 85% for patients ≤ 50 years, 51 to 65 years, and > 65 years, respectively.

ADVERSE REACTIONS

The two studies described **(see Clinical Studies)** evaluated 228 patients with multiple myeloma receiving VELCADE 1.3 mg/m^2/dose twice weekly for 2 weeks followed by a 10-day rest period (21 day treatment cycle length) for a maximum of 8 treatment cycles.

The most commonly reported adverse events were asthenic conditions (including fatigue, malaise and weakness) (65%), nausea (64%), diarrhea (51%), appetite decreased (including anorexia) (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (37%), pyrexia (36%), vomiting (36%), and anemia (32%).
Fourteen percent of patients experienced at least one episode of grade 4 toxicity, with the most common toxicity being thrombocytopenia (3%) and neutropenia (3%).

Serious Adverse Events (SAEs): Serious Adverse Events are defined as any event, regardless of causality that: results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability or is deemed to be an important medical event. A total of 113 (50%) of the 228 patients experienced SAEs during the studies. The most commonly reported SAEs included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

Adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 18% of patients. The reasons for discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), diarrhea (2%), and fatigue (2%).

Two deaths were reported and considered by the investigator to be possibly related to study drug: one case of cardiopulmonary arrest and one case of respiratory failure.

The most common adverse events are shown in **Table 3**. All adverse events occurring at ≥ 10% are included. In the single arm studies conducted it is often not possible to distinguish adverse events that are drug-caused and those that reflect the patient's underlying disease. See discussion of specific adverse reactions following **Table 3**.

360 **Table 3: Most Commonly Reported (≥10% Overall) Adverse Events (N=228)**

Adverse Event	All Patients (N = 228) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events
Asthenic conditions	149 (65)	42 (18)	1 (<1)
Nausea	145 (64)	13 (6)	0
Diarrhea	116 (51)	16 (7)	2 (<1)
Appetite decreased	99 (43)	6 (3)	0
Constipation	97 (43)	5 (2)	0
Thrombocytopenia	97 (43)	61 (27)	7 (3)
Peripheral neuropathy	84 (37)	31 (14)	0
Pyrexia	82 (36)	9 (4)	0
Vomiting	82 (36)	16 (7)	1 (<1)
Anemia	74 (32)	21 (9)	0
Headache	63 (28)	8 (4)	0
Insomnia	62 (27)	3 (1)	0
Arthralgia	60 (26)	11 (5)	0
Pain in limb	59 (26)	16 (7)	0
Edema	58 (25)	3 (1)	0
Neutropenia	55 (24)	30 (13)	6 (3)
Paresthesia and dysesthesia	53 (23)	6 (3)	0
Dyspnea	50 (22)	7 (3)	1 (<1)
Dizziness (excluding vertigo)	48 (21)	3 (1)	0
Rash	47 (21)	1 (<1)	0
Dehydration	42 (18)	15 (7)	0
Upper respiratory tract infection	41 (18)	0	0
Cough	39 (17)	1 (<1)	0
Bone pain	33 (14)	5 (2)	0
Anxiety	32 (14)	0	0
Myalgia	32 (14)	5 (2)	0
Back pain	31 (14)	9 (4)	0
Muscle cramps	31 (14)	1 (<1)	0
Dyspepsia	30 (13)	0	0
Abdominal pain	29 (13)	5 (2)	0
Dysgeusia	29 (13)	1 (<1)	0
Hypotension	27 (12)	8 (4)	0
Rigors	27 (12)	1 (<1)	0
Herpes zoster	26 (11)	2 (<1)	0
Pruritus	26 (11)	0	0
Vision blurred	25 (11)	1 (<1)	0
Pneumonia	23 (10)	12 (5)	0

Asthenic conditions (fatigue, malaise, weakness)

Asthenia was reported in 65% of patients and was predominantly reported as Grade 1 or 2. The first onset of fatigue was most often reported during the 1st and 2nd cycles of therapy. Asthenia was Grade 3 for 18% of patients. Two percent of patients discontinued treatment due to fatigue.

Gastrointestinal Events

The majority of patients experienced gastrointestinal adverse events during the studies, including nausea, diarrhea, constipation, and vomiting. Grade 3 or 4 gastrointestinal events occurred in 21% of patients and were considered serious in 13% of patients. Vomiting and diarrhea each were of Grade 3 severity in 7% of patients and were Grade 4 in <1%. Five percent of patients discontinued due to gastrointestinal events. Appetite decreased (anorexia) was reported as an adverse event for 43% of patients. The incidence of Grade 3 decreased appetite was 3%.

Thrombocytopenia

Thrombocytopenia was reported during treatment with VELCADE for 43% of patients. The thrombocytopenia was characterized by a dose related decrease in platelet count during the VELCADE dosing period (Days 1 to 11) with a return to baseline in platelet count during the rest period (Days 12 to 21) in each treatment cycle. Thrombocytopenia was Grade 3 or 4 in intensity for 27% and 3% respectively of patients. Four percent (4%) of patients discontinued VELCADE treatment due to thrombocytopenia of any grade.

Peripheral Sensory Neuropathy

Events reported as peripheral neuropathy, peripheral sensory neuropathy, and peripheral neuropathy aggravated occurred in 37% of patients. Peripheral neuropathy was Grade 3 for 14% of patients with no Grade 4 events. New onset or worsening of existing neuropathy was noted throughout the cycles of treatment. Six percent (6%) of patients discontinued VELCADE due to neuropathy. More than 80% of all study patients had signs or symptoms of peripheral neuropathy at baseline evaluation. The incidence of Grade 3 neuropathy was 5% (2 of 41 patients) in patients without baseline neuropathy. Symptoms may improve or return to baseline in some patients upon discontinuation of VELCADE. The complete time-course of this toxicity has not been fully characterized.

Pyrexia

Pyrexia (> 38°C) was reported as an adverse event for 36% of patients and was assessed as Grade 3 in 4% of patients.

Neutropenia

Neutropenia occurred in 24% of patients and was grade 3 in 13% and grade 4 in 3%. The incidence of febrile neutropenia was <1%.

406
407 **Hypotension**
408
409 Hypotension (including reports of orthostatic hypotension) was reported in 12% of
410 patients. Most events were Grade 1 or 2 in severity. Grade 3 hypotension occurred in
411 4% of patients; no patient experienced Grade 4 hypotension. Patients developing
412 orthostatic hypotension did not have evidence of orthostatic hypotension at study entry;
413 half had pre-existing hypertension and one third had evidence of peripheral neuropathy.
414 Doses of antihypertensive medications may need to be adjusted in patients receiving
415 VELCADE. Four percent of patients experienced hypotension, including orthostatic
416 hypotension, and had a concurrent syncopal event.
417

418 **Serious Adverse Events from Clinical Studies**
419
420 In approximately 580 patients, the following serious adverse events (not described above)
421 were reported, considered at least possibly related to study medication, in at least one
422 patient treated with VELCADE administered as monotherapy or in combination with
423 other chemotherapeutics. These studies were conducted in patients with hematological
424 malignancies and in solid tumors.
425
426 **Blood and lymphatic system disorders:** Disseminated intravascular coagulation
427
428 **Cardiac disorders:** Atrial fibrillation aggravated, atrial flutter, cardiac amyloidosis,
429 cardiac arrest, cardiac failure congestive, myocardial ischemia, myocardial infarction,
430 pericardial effusion, pulmonary edema, ventricular tachycardia
431
432 **Gastrointestinal disorders:** Ascites, dysphagia, fecal impaction, gastritis hemorrhagic,
433 gastrointestinal hemorrhage, hematemesis, ileus paralytic, large intestinal obstruction,
434 paralytic intestinal obstruction, small intestinal obstruction, large intestinal perforation,
435 stomatitis, melena, pancreatitis acute
436
437 **Hepatobiliary:** Hyperbilirubinemia, portal vein thrombosis
438
439 **Immune system disorders:** Anaphylactic reaction, drug hypersensitivity, immune
440 complex mediated hypersensitivity
441
442 **Infections and Infestations:** Bacteremia
443
444 **Injury, poisoning and procedural complications:** skeletal fracture, subdural hematoma
445
446 **Metabolism and nutrition disorders:** Hypocalcemia, hyperuricemia, hypokalemia,
447 hyponatremia, tumor lysis syndrome

Nervous system: Ataxia, coma, dizziness, dysarthria, dysautonomia, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, transient ischemic attack

Psychiatric: Agitation, confusion, psychotic disorder, suicidal ideation

Renal and urinary: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria urinary incontinence, urinary retention, renal failure, acute and chronic, glomerular nephritis proliferative

Respiratory, thoracic and mediastinal: Acute respiratory distress syndrome, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, respiratory failure

Vascular: Cerebrovascular accident, deep venous thrombosis, peripheral embolism, pulmonary embolism

OVERDOSAGE

Cardiovascular safety pharmacology studies in monkeys show that lethal IV doses are associated with decreases in blood pressure, increases in heart rate, increases in contractility, and ultimately terminal hypotension. In monkeys, doses of 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in progressive hypotension starting at 1 hour and progressing to death by 12 to 14 hours following drug administration.

No cases of overdosage with VELCADE were reported during clinical trials. Single doses of up to 2.0 mg/m^2 per week have been administered in adults. In the event of overdosage, patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure and body temperature **(see PRECAUTIONS and DOSAGE AND ADMINISTRATION)**.

There is no known specific antidote for VELCADE overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of VELCADE is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21) **(see CLINICAL STUDIES section for a description of dose administration during the trials)**.

This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.

Dose Modification and Reinitiation of Therapy:

VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below **(see PRECAUTIONS)**. Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). The following table contains the recommended dose modification for the management of patients who experience VELCADE-related neuropathic pain and/or peripheral sensory neuropathy **(Table 4)**. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk/ benefit assessment.

Table 4: Recommended Dose Modification for VELCADE-related neuropathic pain and/or peripheral sensory neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1.0 mg /m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue VELCADE

NCI Common Toxicity Criteria website – http://ctep.info.nih.gov/reporting/ctc.html

Administration Precautions: VELCADE is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage.

Reconstitution/Preparation for Intravenous Administration: Prior to use, the contents of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection, USP. The reconstituted product should be a clear and colorless solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Stability: Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light.

VELCADE contains no antimicrobial preservative. When reconstituted as directed, VELCADE may be stored at 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Reconstituted VELCADE should be administered within eight hours of preparation. The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to three hours in a syringe, however total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

HOW SUPPLIED

VELCADE (*bortezomib*) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of *bortezomib* as a white to off-white cake or powder.

NDC 63020-049-01	3.5 mg single dose vial

STORAGE

Unopened vials may be stored at controlled room temperature 25° C (77° F); excursions permitted from 15 to 30° C (59 to 86° F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Caution: Rx only.

U.S. Patents: 5,780,454, 6,083,903, 6,297,217

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VELCADE™ (bortezomib) for Injection

Patient Information

VELCADE is intended for use under the guidance and supervision of a health care professional. Please discuss the possibility of the following side effects with your doctor:

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability: VELCADE may be associated with fatigue, dizziness, light-headedness, fainting or blurred vision. Please exercise caution or avoid operating machinery, including automobiles, following use of VELCADE.

Pregnancy/Nursing: Please use effective contraceptive measures to prevent pregnancy and avoid breast feeding during treatment with VELCADE.

Deydration/Hypotension: Following the use of VELCADE therapy, you may experience vomiting and/or diarrhea. Drink plenty of fluids. Speak with your doctor if these symptoms occur and what you should do to control or manage these symptoms.

If you experience symptoms of dizziness or light-headedness, consult a healthcare professional. Seek immediate medical attention if you experience fainting spells.

Concomitant Medications: Please speak with your doctor about any other medication you are currently taking. Your doctor will want to be aware of any other medications.

Peripheral Neuropathy: Contact your doctor if you experience new or worsening symptoms of peripheral neuropathy, such as numbness, pain, or a burning feeling in the feet or hands.